Hello, it is my pleasure to introduce to you a new DARPA program, the Bio-Fluidic Chips program, or BioFlips.

This program is just being started in fiscal year 2000 out of the Microsystems Technology Office.

I am Abe Lee, the Program Manager.

I will be introducing to you the objectives and the approaches of this program and if successful, what military and commercial applications can be realized.

The state-of-the-art biochips today are primarily aimed at high throughput screening and combinatorial chemistry for drug discovery and other genomics' applications. The missing link is sample preparation of raw samples such as body fluids.

The BioFlips program will target sample preparation of complex fluids SUCH as body fluids on a chip-scale. To achieve this, the BioFlips program will focus on new microfabrication platforms that integrate multiple fluidic components onto single chips.

These components can be microstructures, micropumps, microvalves and various other microsensors.

TOTAL CHIP-SCALE INTEGRATION is the ultimate goal of this program.

A second goal of the program is to develop active fluidic chips.

This will be achieved by integrating fluidic transport components with in situ sensors that enable local feedback control in the microchannels.

With Active chips, reconfiguration and self-calibration of the sensing parameters will be made possible. This is very difficult with the passive microfluidic chips available today.

For MEMS-based sensors, the self-calibration capability was the reason it could compete and replace more conventional sensors.

For example, the integrated air-bag accelerometers developed by Analog Devices for the automobile industry had built-in self-calibration that allowed for self-testing prior to starting up the engine.

For BioFlips, self-calibration will be even more important since in real-time sensing the input contains multiple parameters.

These parameters can cause drastic fluctuations and result in poor signal-to-noise ratios.

With built-in self-calibration, the fluidic controller can in real-time adjust the dynamic range of the sensor so that the sensor can be robust in field use.

The MicroFlumes program that ended in fiscal year 1999 has brought to us microscale technologies for fluid transport and microscale-enabled assays.

However, the program focused mainly on the miniaturization of components and not total chip-scale integration.

The goal was to enable hand-held, portable instruments with microfluidic components.

The photo to the left here shows a wafer-scale fluidic motherboard with chip-scale fluidic components bonded onto it that complete a fluidic circuit.

Control electronics were on separate PC boards that were interconnected by wires to the fluidic wafer.

Using this methodology, it is difficult to further miniaturize systems to sizes smaller than handheld instruments.

Performance is also limited by the alignment between components and wafers that result in impedance mismatches AND larger dead volumes.

These factors are barriers that will limit the eventual cost and performance of the instruments.

The BioFlips program will build upon this foundation and enable revolutionary applications through total on-chip integration.

The project illustrated on the right will target 3 orders of magnitude reduction in size and 2 orders of magnitude reduction in power consumption.

On-chip feedback control will enable dynamic assays to be programmed.

In analogy, the BioFlips program will enable integrated circuit-like devices for microfluidic processing as opposed to the breadboard like devices developed by the MicroFlumes program.

Another major distinction is that BioFlips will be focusing on low cost devices (such as plastics) and enable disposable chips for medical applications.

Microfluidics benefits from Miniaturization and Integration.

We are very aware that this is the "the smaller, the better" era as opposed to 30 years ago when everything was judged by how grand and how big the system was.

However, as most of us know, smaller is not always better. This is also true with microfluidics. Fortunately, in microfluidics, there is no inherent showstopper in the scaling down of dimensions.

I like to use the waterbug as an example to illustrate that microscale fluidics is a miraculous phenomena, enabling the bug to "walk on water" by utilizing surface tension to overcome its body weight.

Scaling doesn't change physical laws but it changes the dominant physical parameter.

The microfluidics designer must take advantage of these dominant factors to achieve his or her functional goals.

For example, microchannels are prone to clogging due to high surface-to-volume ratio and microscale flow rates are extremely low.

Also, in microscale, surface tension is high so once bubbles form in the channels, they become very difficult to get rid of. On the other hand, at the microscale, large surface areas enable high target capture efficiencies and laminar flow allows for controlled diffusion and thus controlled reaction rates.

By taking advantage of microscale phenomena, very high sensitivity and high specificity devices that require lower power and less reagents CAN be designed.

Integration of multiple components and multiple functionality on a single chip is POWERFUL, as the integrated circuits (IC) have demonstrated to us.

Integrated fluidics will connect large arrays of components that can be programmed to perform multiple analyses with single devices.

It also eliminates interconnections, dead volumes and sample carry-over, resulting in higher sensitivities and higher signal-to-noise ratios. Batch fabrication results in lowered manufacturing cost.

The two most important tasks for BioFlips are, one, to develop microfabrication processes for on-chip fluidic transport control.

The second task is to develop microfabrication processes for heterogeneous integration of polymeric materials for fluidics and semiconductor materials for optics, electronics and detectors.

For on-chip integrated fluid transport control the major challenge is to develop novel processes that consolidate and streamline the incompatible fabrication processes that are currently needed for each component.

For the integration of plastics with solid-state materials the challenges include the bonding and alignment of these very different functional materials and also the design of optical and electrical interfaces.

As one can imagine, to cram so much function on a chip is a difficult task and truly innovative approaches will be needed.

The key is to consolidate sequential analysis steps through the integration of multifunctional components.

Instead of designing one component at a time, BioFlips will develop microfabrication processes that can incorporate the layout of interconnected fluidic components in the form of an integrated chip.

By focusing on this top-down integration approach we develop general platforms that will allow the designer to lay out and model complex fluidic circuits for multiplexed bioassays.

It is possible that in the near future, microfluidic fabrication foundries will be established such as the CMOS foundries are today for the IC industry.

Through integration and new packaging technologies, BioFlips will enable the processing and sensing of biofluids in compact formats, eventually approaching wristwatch sizes.

The technologies developed in this program will be primarily demonstrated through body fluids assays, such as blood, interstitial fluids, and perspiration.

The sample acquisition interfaces will take advantage of recent developments in glucose diagnostics for diabetics.

Examples include microneedles, ultrasonic pumping, and micro thermal ablation.

These methods can all be integrated onto fluidic chips.

On the other hand, the reverse of sample collection INTO the chip is fluidic delivery OUT of the chip.

BioFlips will enable the transdermal delivery of drugs or other reagents back into the body with precise dosage control.

A total integrated BioFlip could complete a feedback loop including all three, body fluids sampling for diagnostics, drug delivery for therapeutics, and the integrated microfluidics to process and connect the two.

Here I'm going to describe two projects funded by BioFlips.

The top example is a novel fluidic control element.

The microfluidic channels are formed by plastic molding processes and the circular elements are subsequently generated by flushing through precursor monomers that are then patterned by UV light polymerization.

The polymers chosen are functionalized hydrogels that react to parameters such as pH and temperature.

These hydrogels can also be developed to expand or contract specifically to biological agents such as various proteins and antigens.

This particular diagram illustrates a possible logic element.

The two circular components are hydrogel control elements that respond, for example, to different pH values.

In this diagram, if the left hand element expands in low pH and the right hand one contracts in high pH, then the fluid path will open to the right with acidic samples and open to the left with base samples.

This simple component is multifunctional since it is a sensor and an actuator, a valve and a pump.

Furthermore, hundreds or thousands of these components can be integrated on a single chip.

As a result, many different bioassays can be carried out with virtually no power.

The second example illustrates a total BioFlip for host-based assays.

It includes sample collection via microneedles, sample transport through the horn-shaped conduit, sample preparation via fluidic manifolds, and also integration of readout all on a 2- 3 cm footprint.

The integration platform utilizes PZT actuation, allowing for local control of fluid transport by generating acoustic gradients through PZT pillar arrays.

The technology developed will enable a wide variety of applications, covering military and the commercial sectors.

Futurists in DoD are calling for presymptomatic detection of infection as early warning of epidemic outbreaks.

Whether caused by nature or by terrorists, the goal is to provide for ample time windows for effective therapeutics.

One application of the BioFlips program will be very compact health status indicators to be worn by warfighters.

These indicators can be monitored at a central location while the warfighters remain mobile and can carry out their operations in buildings or wherever the mission calls for, which is very important in modern warfare.

These devices could also aid in combat casualty care for the military.

Another potential application is for the triage of large-scale incidents after terrorist attacks on major events such as, God-forbid, the Olympics.

Other applications include water and food testing, rapid blood safety analysis of donors, especially in third world countries, and on-demand drug delivery.

There are also numerous medical applications. An example is the continuous monitoring of high-risk patients, either the chronically ill or post-surgical.

Another new DARPA program that also started in FY2000 is the Program on "Fundamental Research at the Bio:Info:Micro Interface".

This is a program led by Program Managers in 3 offices, MTO, DSO, and ITO.

I represent the Micro portion of this program.

The main goal is to exploit the intersection of biology with DARPA's traditional strengths in microsystems and information technology for future defense applications.

During the first phase of this program, fundamental research is solicited in order not to limit the scope of the proposals and therefore only universities are invited to participate as prime grantees.

An important goal is to train the next generation of researchers at the intersection of these three fields.

I am interested in chip-scale technologies for the control of molecular flow in chip-scale devices.

A goal is to quantify signal transduction between individual cells, proteins, and nucleic acids and connect them to computational data base searches and analyses.

Currently, there is no way to detect dynamic protein interactions in real-time.

A far-out application is to perform in vitro human tests with human cell components.

To conclude, BioFlips is a new program that will focus on the total integration of on- chip functionality. This program is truly at the intersection of biotechnology and microtechnology.

Thank you for your attention.

I look forward to meeting you at the MTO booth.

If we don't meet and you have questions for me, please email me at aplee@darpa.mil